Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 1, pp. 6–11, 2002

0360-3016/02/$–see front matter

ELSEVIER

PII S0360-3016(02)02718-9

NCI RADIATION RESEARCH PROGRAM MEETING REPORT

NEW DIRECTIONS IN BRACHYTHERAPY

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INTRODUCTION

A one and one-half day workshop to assess the current state of the science in brachytherapy was convened at the request of the Radiation Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute. The advances in the knowledge of the molecular biology of the radiation response, and in biologic imaging, image fusion, and computer technology made this an appropriate time to address the state of the science and research opportunities for brachytherapy. The aspects of brachytherapy that make it unique include the ability to choose a wide range of dose rates and energies not available with teletherapy, and the ability to precisely localize the placement of radiation sources within tumor, or portions of the tumor. The agenda included both the biology and physics related to brachytherapy. Much of the first day was devoted to overviews of clinical and research topics. The participants then separated into two breakout sessions. Appendix I includes the workshop participants. The following morning session included a presentation and discussion of each breakout session and recommendations for future research. Some research recommendations are specific for brachytherapy and others are more general, as noted.

BRACHYTHERAPY BIOLOGY (SIMON POWELL, M.D.—CHAIR)

The sense of the meeting was that the knowledge of current biology applied to the specific biologic questions posed by brachytherapy represents an area in which innovative research can be achieved and translational work can be encouraged. The consensus was that the use of brachytherapy in cancer therapy was increasing, not decreasing, and, therefore, support for research to understand the biology of brachytherapy should be encouraged.

Dose-rate dependence and biologic modeling

The widespread use of the alpha-beta ratio in radiation biology during the past decades may have particular relevance for high-dose-rate (HDR) and low-dose-rate (LDR) brachytherapy. Experience has been gained from the use of widely differing dose rates in the intracavitary treatment of carcinoma of the cervix. However, little of this knowledge has been applied to other tumor sites. Currently, prostate brachytherapy gives continuous LDR brachytherapy with permanent indwelling ^{125}I or ^{103}Pd seeds. However, for brachytherapy as the sole treatment of carcinoma of the breast, in which the affected quadrant is the only treated volume, both HDR and LDR brachytherapy have been used. Currently, the data for dose and dose-rate equivalent effects are insufficient.

Recommendation 1: There should be further research on modeling the dose-rate effects of radiation and on how these effects are affected by volume. Bioeffect modeling for brachytherapy is necessary and a physical dose alone is insufficient because:

1. The biologic effectiveness of a brachytherapy regimen depends on the dose rate
2. Brachytherapy is often combined with teletherapy, and the dose rate and fractionation scheme needs to be considered
3. Brachytherapy often replaces teletherapy and equivalent doses need to be determined, which requires the use of a bioeffect model
4. HDR brachytherapy is beginning to replace LDR, so equivalent doses need to be calculated, and this also requires bioeffect modeling

Recommendation 2: Outcome reporting in brachytherapy should be standardized. Regarding physics data, the needed quantities are three-dimensional (3D) dose distributions in the relevant structures. The more common dose–volume histogram is a poor substitute for this fully descriptive mode of reporting. With clinical data, the usual indicators (e.g., disease-free survival) must be reported as a function of time from treatment. Bioeffect models need to be developed and tested, and parameters derived, by retrospective analysis of outcomes related to 3D dose distributions in tumors and

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Received Dec 19, 2001. Accepted for publication Dec 21, 2001.

normal tissues. Sophisticated outcome analysis tools and resources need to be developed and supported. A central registry may be the only practical way of accumulating sufficient data for this type of modeling. Such a database should contain not only information about the tumor but about the relevant normal tissue and tumor vasculature.

Enhancement of brachytherapy response

Recommendation 3: Biologic response modifiers for brachytherapy should be explored. Exploiting both the brachytherapy procedure and the limited volume of tissue irradiated, intratumoral drug delivery of chemotherapy, cytokines, or viral-derived gene therapy can be considered. In some cases, there could be relative tumor specificity in the mechanism of action, but in others, the specificity is achieved merely by the intratumoral delivery route. Although some aspects of this work are not unique to brachytherapy, the use of cytotoxic cytokines and antiangiogenesis agents could be well suited to the field of brachytherapy. Research in understanding the optimum timing of the use of these modifiers with either HDR or LDR brachytherapy is needed.

Another example of radiation enhancement is the use of hyperthermia. Although hyperthermia is considerably reduced in its application, the reason for the failure of hyperthermia was largely the inability to heat deep-seated tumors to the target temperature. Given the restriction in the target volume used in brachytherapy, there would now be better options for the local heating of tumors or tumor beds, amenable to brachytherapy. Relative tumor specificity could be further enhanced by a combination of both hyperthermia and heat-activated gene therapy. A better understanding of the molecular mechanisms of the heat-activated stress response now allows this potential mechanism of sensitization to be exploited further.

Genetic determinants and tissue acquisition

Recommendation 4: The dynamics of the tumor and normal tissue to radiation should be investigated.

Molecular and genetic analysis. Specific molecular determinants of radiation sensitivity are the subject of many ongoing studies. There is precedent for some of these factors to have specific dose-rate effects. For example, the dose-rate sparing effect for ataxia-telangiectasia cells is relatively little compared with wild-type cells. Given the wide variety of genetic alterations that contribute to radiation sensitivity, understanding the dose-rate dependence of these known genetic factors would be considerably important. In particular, genetic alterations in tumors frequently result in a disruption of genome stability, and some of these factors will have a significant consequence for radiation response. An understanding of the genetic factors directly involved in DNA repair or those involved indirectly by cell cycle regulation would be of considerable interest in relation to dose-rate dependence. The genetic differences between tumor cells and normal cells provide not only a potential therapeutic strategy for virus-derived gene therapy; they also allow specific additional strategies for radiation sensitization.

Tissue acquisition. One clear advantage of brachytherapy, in relation to tumor biology, is the ability to obtain samples of tumor tissue because of the procedure. This reflects a unique opportunity to obtain sequential biologic samples during therapy, which is not easily achieved in other types of radiotherapy (RT). The use of these biologic samples for gene-expression analysis using microarrays, DNA microchips and other new developing technologies may provide an important insight into how a tumor responds to the immediate effect of RT. A comparison of real-time dosimetry vs. biologic dosimetry is also feasible. The role of hypoxia, interstitial tumor pressure, and other aspects of the tumor microenvironment can also be continuously monitored during therapy. Thus, there is a unique opportunity to study the dynamics of the response to RT using brachytherapy.

BRACHYTHERAPY PHYSICS (SUBIR NAG, M.D.—CHAIR)

Improved imaging

Recommendation 5: Support functional and biologic imaging research and the incorporation of such information into treatment planning. There is considerable enthusiasm for encouraging further research in functional biologic treatment planning. In this process, the tumor volume is defined physically, by the best combination of conventional imaging modalities, and biologically, using magnetic resonance spectroscopy (MRS), positron emission tomography (PET), radioimmuno-guided techniques, or methods yet to be developed. There have been preliminary attempts to use PET technology for biologic imaging, especially in patients with lung cancer. The limiting factor at this time is spatial resolution. The use of MRS and the relationship between a spectral image and tumor burden is still unclear. The use of functional MRI to monitor not only blood flow but also oxygen consumption is now feasible. The use of this technology should be considered to develop the concept of conformation of the dose distribution to the biologic treatment volume and not just the anatomic treatment volume.

Of recent interest is the development of molecular imaging of a tumor. An example of the potential capability of this technology is the ability to identify cell-surface molecules and use ligand binding with a ferromagnetic tag to generate a biologically based MR image. Other techniques are being developed to image gene therapy. A particular application of this technology pertinent to brachytherapy may be to use high-resolution surface or endocavitary coils to improve the quality and resolution of the image.

Recommendation 6: New techniques for anatomic localization of target volume should be developed. The target volume is currently generally defined using radiologic imaging (e.g., plane radiography, CT, MRI, bone scan). The improvements required include increased tissue resolution; improved boundary definition; functional imaging (i.e., PET and MRS); and antibody-based imaging.

Radiographs are conventionally used for source localization and calculation of the dose distribution around brachytherapy applicators, whether they are placed manually or with a computerized treatment planning system. The doses to normal tissues such as the bladder and the rectum have traditionally been calculated from the implant localization films with contrast in the bladder or catheter bulb and a radiopaque marker or contrast in the rectum. The inability of the orthogonal film pair method to delineate organ boundaries diminishes the reliability of the normal tissue dose point determinations and compromises the understanding of the dose distributions to the nonopacified soft tissues. An improvement in the spatial resolution may also bring about improved target volume definition of the imaging modality and fusion of various imaging modalities (e.g., transrectal ultrasonography with MRI or CT).

Although there are limitations in defining the target volume for gross tumors, it is even more difficult to define the clinical target volume after resection, because there is no gross residual tumor to visualize or image. In these circumstances, it may be possible to detect the clinical target volume by injecting a radiolabeled antibody and detecting the occult tumor by scanning the tumor bed with a gamma-detecting probe during surgery. Radiolabeled antibody scanning may also be used to delineate the uptake that should correspond to the areas containing the tumor and to dose-intensify these areas, as has been done in prostate cancer.

The integration of 3D imaging into the planning and delivery of brachytherapy, and also exploiting functional imaging to assess local response to brachytherapy, lags far behind external-beam RT, for which image-guided therapy is under active development. Modern 3D imaging cannot be fully exploited for these purposes because of the unique characteristics of brachytherapy (i.e., steep dose gradients and surgical manipulation of the target volume and surrounding normal tissues associated with the insertion of applicators, needles, or seeds).

Real-time treatment planning

Recommendation 7: Techniques for efficient deformable image registration should be developed. Soft-tissue deformation, directly or indirectly associated with the brachytherapy insertion procedure, is the most formidable obstacle to the meaningful application of 3D imaging in the planning and guidance of brachytherapy. The changes in target volume, critical organ shape, and relative location due to applicator insertion invalidate the pretreatment 3D imaging studies used to design the implant geometry, select the prescribed dose, and guide the applicators into position. Examples of the soft-tissue deformations that confound planning include

1. Needle insertion and prostate edema occurring during the prostate implant procedure, which invalidate the pretreatment volume study and, as a result, the needle insertion trajectories.
2. Insertion of a transrectal ultrasound probe and postimplant prostate edema, which changes the target volume geometry relative to the choline/citrate ratio MRS scans obtained before implantation.
3. Prostate edema accompanying transrectal ultrasound-guided permanent seed implants, which results in rapid onset of swelling that gradually resolves during a 10–30-day period. This causes both the instantaneous dose-rate distribution, plus the spatial location of each tissue voxel, to vary with time.
4. Deformation of pelvic soft tissues caused by insertion of intracavitary applicators and regression of gross tumor volume during the treatment course. These make it impossible to add dose contributions from the multiple brachytherapy insertions or to register external beam treatments to an anatomically consistent frame of reference.

To solve the problem posed by these examples, voxel-to-voxel mapping between pairs of serial imaging studies is needed. For prostate edema, deformable registration techniques could be used to predict the relative positions of the target tissue voxels and seeds as a function of time, so that the integrated total dose received by each tissue voxel could be rigorously determined. Finally, pairs of images taken before and after a tissue-deforming intervention could be matched.

Clearly, the rigid image alignment techniques currently used in RT planning are unable to adapt to localized tissue displacement and deformation. One promising class of algorithms uses continuum mechanics models to describe the deformation process. Another approach to this problem has been the application of the more complex viscous fluid transformation model to the problem of calculating cumulative dose in definitive RT for cervical cancer. The application of these approaches has been largely limited to the brain, in which contrast between tissue types is high and image intensity within anatomically distinct regions is uniform. Unsolved research problems include adapting the technology to low-contrast imaging modalities such as CT outside the brain and to multimodality image fusion in nearly all sites. Other problems include *in vivo* verification of the tissue correspondence predictions of these models and measurement of the underlying biomechanical tissue properties.

The lack of efficient and accurate automated tools for segmenting soft-tissue structures is impeding the use of intraoperative, image-guided brachytherapy. Currently, it is necessary to repeatedly image the patient during the operative procedure, both to guide the needles and applicators to the prescribed locations and to compensate for associated soft-tissue deformation. To use this imaging data to update dosimetric calculations and to correct needle insertion, the relevant anatomy must be contoured. The volume of imaging data acquired precludes manual segmentation. No satisfactory and general automated methods have been developed to date, but they are needed.

Improved treatment delivery, applicator integration, and treatment verification

Recommendation 8: Novel brachytherapy applicators that allow the integration of imaging information should be developed. Computerized treatment planning software using CT scans rather than radiographs to plan brachytherapy is available. These CT-based methods have accurately localized intracavitary and interstitial applicators and showed the 3D anatomic relationship of the applicators, uterus, and neighboring structures. Unfortunately, the standard applicators used for intracavitary and interstitial radiation are made of metal, which can cause streak artifacts on CT images that make determining the tumor volume and normal anatomy difficult. The tandem position, uterine wall thickness, and distance to the rectosigmoid and bladder can be seen. Appropriate level and window settings assist visualization. Plastic and other CT-compatible applicators have subsequently been used at a few institutions to decrease streak artifacts, but these are expensive, if commercially available at all, or must be fabricated at individual institutions. The bladder and rectal doses obtained from localization films have been noted to be appreciably lower than the CT-calculated doses. MRI may hold future promise for imaging brachytherapy applications. The value of MRI in imaging gynecologic malignancies lies in its multiplanar capability and superior contrast resolution, which can facilitate assessment of cervical tumor size and volume, distinction of the tumor from normal uterus and cervical tissue, and definition of parametrial and vaginal infiltration of disease. Unfortunately, the inability to obtain good quality MRI scans with the traditional metal afterloading applicators used for intracavitary and interstitial implantation has discouraged the use of MRI for brachytherapy treatment planning. Although some commercial vendors have fabricated Food and Drug Administration–approved MRI and CT compatible intracavitary gynecologic applicators, only a few institutions are using them. Few computer software programs accurately and reliably integrate and manipulate MR images within existing brachytherapy planning systems.

Recommendation 9: Real-time, in vivo dosimetry systems should be investigated. Another possibility to improve delivery and dosimetry is to incorporate mini-dosimeters or diodes within brachytherapy applicators or needles to autodetect the source position as they are being deposited; the information obtained could be used to update the dose calculation. This would provide real-time dosimetry data. Another intriguing method to obtain dosimetry would be to develop smart seeds containing computer chips that could emit unique signals that could be detected outside the patient, allowing seed localization independent of the imaging modality used.

Minimally perturbing systems and robotic delivery systems

Recommendation 10: Explore techniques to improve and standardize the brachytherapy procedure. The insertion of various applicators in or near the intended target often results in changes in the target geometry. These changes, and their evolution in time, must be anticipated and corrected for in the treatment plan. In particular, the process of treatment delivery must be as operator-independent as possible. For instance, in permanent prostate implants, the intended seed positions and their actual locations in the gland are known to vary. Image tools that could reconstruct in real time the positions of seeds already inserted could be used to reoptimize the plan.

A motorized device could automatically push the needle tip into position at a predetermined distance within the target volume to simplify the implant procedure. Optical encoders would show the needle position and recalculate the dosimetry in real time. This would allow automatic robotic placement of sources within the target volume to reduce operator dependence. The robotic source insertion could be combined with recent noninvasive and minimally invasive surgical techniques to decrease tissue trauma.

Brachytherapy sources

Recommendation 11: Develop new radioactive sources to address specific clinical settings. Currently available ^{137}Cs and ^{192}Ir sources have photon energies ranging from 400 to 660 keV. At energies $>$150 keV, essentially all radionuclides have similar penetration in tissue. The shielding requirements rapidly increase with increasing energy; therefore, the cost of radiation protection rapidly increases with higher energies. The need for shielding is reduced for energies $<$120 keV. A major rationale for investigating new low-energy brachytherapy sources, such as ^{241}Am, ^{169}Yb, and ^{145}Sm is the ease with which sensitive tissues can be shielded from low-energy photons. This offers the possibility of improving a therapeutic outcome by customizing normal tissue shielding for each patient to achieve an optimal dose distribution.

The requirements for the ideal radioisotope for brachytherapy therefore depend on its purpose. An ideal removable source should have photon energies in the 20–100 KeV range to reduce radiation exposure and a long half-life so that it can be reusable. For remote afterloading use, it should also have a high specific activity to allow a HDR within a small source design. For most tumors, radioisotopes for permanent brachytherapy should have a short half-life. If the half-life is more than a few days, the energy must be low ($<$60 keV) to avoid radiation hazards. However, if the half-life is too short (a few days) it would necessarily have an unacceptably short shelf-life during which it would have to be used. Further exploration is encouraged in these areas.

Neutrons also offer potential in enhancing the tumor response. Neutron brachytherapy with ^{252}Cf has a long history but is still little used. This is due to radiation safety issues and the enhanced effects of neutrons on normal tissue in addition to the tumor. It may be possible to combine ^{252}Cf with a protective radiation modifying agent to overcome the latter problem. It is also possible to use thermal neutrons to activate a previously implanted nonradioactive source. This is similar to using thermal neutrons with a

systemic agent as in neutron capture therapy (BNCT), but the toxicity is limited by the localized distribution of the implant source and is not limited by the intratumoral uptake of boron. This is still in the conceptual stage, and several technical problems need to be solved before it can be put into practice. This would include transport of thermal neutrons to deep body sites and the accurate prediction of neutron flux, activation rates, and final doses delivered.

Treatment planning and dosimetry

Recommendation 12: Explore the use of applied mathematics and optimization tools for plan optimization. Much treatment planning in brachytherapy continues to be performed suboptimally, that is, by manual (trial-and-error) methods, and optimization is mostly limited to identifying the relative dwell weights that optimize coverage and uniformity. Applied mathematics has a well-developed repertory of optimization tools that could be implemented in treatment planning software. Research should continue to incorporate in treatment planning tumor control probability and normal tissue complication probability (TCP/NTCP) information for all structures of interest. Plan optimization would be then done based on an overall figure-of-merit, rather than dosimetrically, as currently done. Before this can be fully trusted, however, much greater knowledge of the dose-time-volume response of both tumor and normal tissue is needed. Furthermore, software that identifies the optimal needle trajectories and seed/dwell position coordinates is required. The deforming effects of seed/needle insertion must be accounted for through dynamically updated planning images through intraoperative imaging and biomechanical modeling.

Most brachytherapy procedures are currently being done using target volume information obtained several days to weeks before implantation. However, target volume alterations could occur in the interim or the target volume could have been deformed by the very act of needle or applicator insertion. Therefore, it is important to image the target volume and guide the brachytherapy applicators in real time, as previously mentioned.

The complexity of modern brachytherapy delivery systems (e.g., remote afterloading systems), while making customization and optimization a reality, also creates many new pathways to inaccurate or incorrect treatment delivery. More modern fail-safe systems for redundantly confirming the accuracy of the administered treatment are necessary. In image-guided brachytherapy, the demands on these tools are increased by the more exacting geometric targeting tolerances and the need to confirm source location relative to soft-tissue anatomy and external and bony landmarks. An unsolved problem of this type is measuring and accounting for organ and applicator motion during LDR brachytherapy. A promising solution to a related problem, verifying that the programmed path of an HDR brachytherapy source is correctly executed, is use of pinhole radiography to measure the HDR source trajectory through space and time.

To make the specification of treatment delivered with quantitatively accurate absorbed dose estimates a reality, more sophisticated algorithms based on Monte Carlo simulation are needed. Promising approaches include novel variance reduction techniques to accelerate conventional Monte Carlo calculations or discrete ordinates simulation, a deterministic solution of the radiation transport equation. Another necessary development is the noninvasive measurement on a voxel-by-voxel basis of attenuation coefficients and other radiologic data needed for Monte Carlo calculations.

Two underdeveloped areas concerning primary dosimetry standards, maintained by the National Institute of Standards and Technology (NIST), deserve mention in this report. First, support should be given to development of a primary air-kerma strength standard for HDR ^{192}Ir sealed sources. Unlike other photon-emitting brachytherapy standards, HDR sources are calibrated against a secondary standard derived by interpolating between NIST's external beam air-kerma standards for ^{137}Cs teletherapy and hard orthovoltage. Finally, the primary standard for an absorbed dose in tissue near the surface of sealed β-emitting sources needs improvement. The current standard, based on an extrapolation ion chamber maintained by NIST, has an uncertainty of 15% and is inadequate for quantitative specification of dose delivered in brachytherapy.

CONCLUSIONS

There are many ongoing areas of investigation in cancer biology and RT planning and delivery that are applicable to brachytherapy, such as molecular and genetic studies of cancer, the molecular and cellular changes induced by radiation, the development of molecular targets for cancer therapy, imaging, and mathematical analysis. Brachytherapy provides unique opportunities and challenges by virtue of the invasiveness of the procedure and the focal distribution of radiation dose.

The research and development recommendations presented in this workshop can be approached through the current mechanisms available for research support. Links to these mechanisms may be found on the Radiation Research Program website (http://www.nci.nih.gov/rrp/opps.htm). Consideration should be given to collaborative programs among radiation oncology, biology, and physics investigators and between radiation oncology and other disciplines, taking advantage of the unique features of brachytherapy.

Follow-up of this workshop should occur through combined efforts of the radiation oncology and medical physics societies. Future brachytherapy meetings should include topics such as biology, imaging, and treatment optimization. A repeat of this workshop should be considered within a few years to assess the progress in the above recommendations and to discuss any barriers to progress for which the Radiation Research Program or the radiation oncology societies can provide assistance.

APPENDIX I

Workshop participants

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